UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,682	12/14/2005	Takaki Koga	14875-147US1 C1-A0226P-US	5413

26161 7590 09/28/2007
FISH & RICHARDSON PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
09/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,682	KOGA ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12/14/05, 6/20/06, 3/22/07, 5/2/07.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-10, 13, and 14 drawn to antibodies that inhibit PCI, in the reply filed on July 17, 2007 is acknowledged.

Claims 11 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on July 17, 2007.

Claims 1-10, 13, and 14 are under examinations as they read on antibodies, compositions, and kits comprising anti-PCI antibodies.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. An example of a hyperlink can be found on page 7 of the disclosure.

Information Disclosure Statement

3. Applicant's IDS forms received 12/14/05, 5/22/06, 6/20/06, 3/22/07, and 5/2/07 have been considered. It is noted that the 5/22/06 IDS indicates that copending application 10/522,086 has overlapping inventors and claims related subject matter but this communication does not comprise information on form 1449. As such the claims of application 10/522,086 have been considered for double patenting issues but no form for this date has been signed for inclusion with this office action.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-10, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosure of the instant specification is not sufficient to enable a skilled artisan to practice the claimed invention without conducting an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Regarding in vivo methods or recited intended results which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Further, in Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art

would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

Applicant has claimed antibodies that bind protein C inhibitor (PCI) and inhibit its biological activities, as well as compositions and kits comprising such antibodies. The anti-PCI antibodies, compositions, and kits are also recited as being useful for treating and preventing numerous diseases characterized by hypercoagulation, such as disseminated intravascular coagulation (DIC). Figure 4 discloses that antibodies made by applicant inhibit PCI activity in purified in vitro systems, but no in vivo data is disclosed. In addition to the anti-PCI antibodies themselves being used to treat various diseases, applicant has claimed compositions and kits comprising anti-PCI antibodies and protein C (either activated (aPC) or unactivated (PC)) for use in treating the same diseases. No data concerning the efficacy of compositions comprising anti-PCI and aPC/PC appear to be disclosed. The breadth of the claims further read on not just the anti-PCI antibodies tested in Figure 4 but also on variants and other antibodies that are "functionally equivalent" to the antibodies recited by name or SEQ ID number.

First, it is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and

conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., Immunobiology, third edition, 1997, pages 3:7-3:11, see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al. PNAS USA, 1982, 79:1979-1983, see entire document, particularly the abstract and the middle of the left column of page 1982). Note that CDRs that are "functionally equivalent" read on mutant sequences comprising insertions, deletions, and substitutions, as well as sequences that are completely unrelated yet comprise the same biological activities. Therefore, "functionally equivalent" antibodies need not comprise any amount of sequence identity or similarity to the recited SEQ ID numbers. As such, it does not appear that antibodies which comprise less than 6 specified CDRs comprise sufficient structural information to maintain binding to PCI since the other CDRs can essentially comprise random sequence, it is known that all CDRs are important for antigen binding, and that single point mutations can disrupt antigen binding. Further, the placing of CDRs outside of their appropriate structural and spatial relationships is not reasonably expected to yield antibodies which maintain binding to tissue factor and the specification does not provide working examples wherein such mixing and matching of CDR sequences at random was performed.

The instant claims also recite that the claimed antibodies, compositions and kits are to be used to treat and prevent various diseases. Prevention encompasses 100% efficacy in 100% of patients to whom the claimed products have been administered. Therapeutic agents are rarely so efficacious, and as has been previously stated the instant specification does not appear to disclose any in vivo efficacy data. It is known in the prior art that aPC is an effective agent that is to be administered to patients to treat discords such as DIC (Griffin et al., US Patent 5,279,956, see entire document particularly the paragraph spanning columns 26 and 27). As disclosed by Fujita et al in US Patent 5,948,752, administration of PCI is also useful in treating patients suffering from hypercoagulation, such as DIC (see entire document, particularly the in vivo model disclosed in Example 3 and claims 1-3). Based on the teachings of the prior art, a

skilled artisan would expect that compositions comprising aPC and PCI would be useful for treating DIC and other hypercoagulation disorders. Applicant has claimed compositions wherein aPC is administered with an antibody that inhibits PCI. As such, administering the anti-PCI antibodies of the instant specification to a DIC patient is essentially equivalent to removing PCI from said patient, yet based on the in vivo data of Fujita et al. a skilled artisan would know that a DIC patient requires more, not less, PCI activity. Again, applicant has not provided any in vivo data demonstrating that the claimed antibodies and compositions comprise the recited therapeutic activity in patients suffering from hypercoagulation disorders such as DIC.

Further, claim 3 recites antibodies that compete with antibodies selected from the group consisting of PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6, and as such these antibodies are a required element needed to make and use the claimed invention. As a required element, these antibodies must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent cell line. See 37 CFR 1.801-1.809.

The instant specification does not appear to disclose that cell lines secreting the recited antibodies have been deposited under the Budapest Treaty or provide assurances that the recited material will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, and that said material will be replaced if the material becomes unviable.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6 have been deposited under the Budapest Treaty and that PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6 will be irrevocably and without restriction or condition released to the public upon the issuance

of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample or for the enforceable life of the patent, whichever is longer. See 37 CFR 1.806 and MPEP 2410-2410.01. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the vector described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of working examples, the unpredictability of the art, and the breadth of the claims, a skilled artisan would be required to perform undue trials and errors to make and use the claimed invention.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1-5 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Specifically, PCI is a naturally occurring protein, and as such antibodies that bind PCI and comprise the recited functional

properties could spontaneously arise in an organism, such as a human, without the deliberate intervention of an inventor. As such, the claimed antibodies appear to be products of nature. Note that the scope of the claims are not limited to specific named clones or SEQ ID numbers in dependent claims due to the recitation of "competes for binding with" in claim 3 and "functionally equivalent thereto" in claim 4. Amendment of the claims to recite that the antibodies are purified or otherwise isolated would demonstrate the hand of man in the claimed invention and would be beneficial in obviating this rejection.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 2, 3, 4, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Meijers et al (of record) as evidenced by Elisen et al. (of record).

Meijers et al. disclose monoclonal antibodies that bind protein C inhibitor (PCI) and inhibit the ability of PCI to inactivate activated protein C (aPC) in purified systems and in plasma (see entire document, particularly the abstract). These antibodies are disclosed as being present in a composition comprising Tris buffer, a known pharmaceutically acceptable carrier (see particularly the right column of page 1401).

Additionally, given that the antibodies of Meijers et al. comprise the recited functional activities, given that antibodies PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6 also comprise these activities, and given that the functional properties of antibody binding to an antigen are determined by the antigen epitope that is bound by the antibody, the antibodies of Meijers et al. and antibodies PC19G8, PC23A7, PC23D8, PC30G1, PC31E2, PC31F1, and PC39C6 compete for the same antibody-binding site because the functional consequences of antibody binding

are the same. Further, given that the antibodies of Meijers et al. comprise the recited biological activities, the antibodies of Meijers et al. are "functionally equivalent" to the antibodies that are recited by SEQ ID number in claim 4.

It is noted that Meijers et al. did not test their antibody for blocking interactions of PCI with thrombin/thrombomodulin. However, the instant specification discloses that the binding sites on PCI for aPC and thrombin overlap (see particularly page 13) and Meijers et al. disclose that their antibody inhibited PCI in plasma which comprises thrombin and thrombomodulin. Further, the prior art of Elisen et al. discloses that the major function of PCI in plasma during coagulation is the inhibition of thrombin (see entire document, particularly the abstract). Given that clotting activity increases in the assays of Meijers et al. subsequent to antibody administration in plasma, the prior art disclosure of Elisen et al. that the major role of PCI in plasma is to inhibit thrombin, and the facts that aPC dissolves clots whereas thrombin generates clots, the anti-PCI antibodies of Meijers et al. must also inhibit interactions between PCI and thrombin based upon the reported experimental data of Meijers et al. As per MPEP 2112, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 2, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijers et al (of record) in view of Kovari et al. (Structure, 1995, 3:1291-3).

The disclosure of Meijers et al. has been discussed above, and differs form the instant claimed invention in that they do not disclose antibody fragments.

Kovari et al. disclose that antibody fragments are useful in obtaining crystals for structure determination studies because binding of antibody fragments, such as Fab, to the target antigen can effectively transform aggregated material into a soluble, monodisperse sample suitable for crystallization and that some proteins can only be crystallized when present in a complex comprising an antibody fragment (see entire document, particularly the left column of page 1291). They further disclose that solving the x-ray diffraction pattern of the resultant crystal is aided by the fact that the antibody fragment can be used for molecular replacement or as a recipient of heavy atom labels (see particularly the right column of page 1292).

Therefore, a person of ordinary skill in the art would have been motivated at the time the invention was made to make well known antibody fragments, such as Fab, from the antibodies disclosed by Meijers et al. so that the antibody fragments could be used in methods of determining the three dimensional structure of PCI using the methods disclosed by Kovari et al.

12. No claims are allowable.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
September 19, 2007